This Week in The Journal

Cellular/Molecular

Protons at Work in the Synaptic Cleft

Synaptic Cleft Acidification and Modulation of Short-Term Depression by Exocytosed Protons in Retinal Bipolar Cells
Mary J. Palmer, Court Hull, Jozsef Vigh, and Henrique von Gersdorff (see pages 11332-11341)

Protons are released during exocytosis as a byproduct of the fusion of vesicles acidified by the proton pumps required for transmitter uptake. These protons have not usually been considered as signaling molecules, although protons can open specific ion channels and modulate other channels involved in synaptic transmission. For example, in photoreceptor ribbon synapses, protons inhibit L-type voltage-gated calcium channels. In this issue, Palmer et al. directly record from the nerve terminals of retinal bipolar cells in goldfish to examine whether protons affect exocytosis. L-type calcium currents were transiently inhibited with a time course that matched exocytosis. When paired stimuli were examined, the size of the calcium current and the amount of exocytosis, measured as a change in membrane capacitance, were greater during the second pulse in physiological buffer conditions (bicarbonate). Thus protons released during the first pulse reduce both calcium influx and the corresponding vesicle release, so that a subsequent depolarization allows more calcium influx and more release. The authors used changes in paired-pulse depression to estimate that cleft pH transiently drops from 7.5 to 6.9. Thus protons provide an activity-dependent means to alter release at this ribbon synapse.

Development/Plasticity/Repair

The Netrin Receptor and a PDZ-Mediated Interaction

Surface Expression of the Netrin Receptor UNC5H1 Is Regulated through a PKC-Interacting Protein/Protein Kinase-Dependent Mechanism
Megan E. Williams, Sareina C.-Y. Wu, William L. McKenna, and Lindsay Hinck (see pages 11279-11288)

Netrin-1 directs migrating neurons and axon growth cones, but the signal it delivers depends on the receptor complex that it activates. Specifically, the receptor DCC promotes attraction, whereas DCC coexpressed with UNC5H1 promotes repulsion. Now Williams et al. identify a functional binding complex of DCC, UNC5H1, and PICK1 (protein interacting with C-kinase-1) that can be modified by PKC. Interestingly, the PDZ domain of PICK1 interacts with the extreme C terminus of UNC5H1. If this sounds familiar, a similar complex forms between PICK1 and AMPA-type glutamate receptors, with apparently similar consequences. PKC activation by the phorbol ester TPA caused UNC5H1 internalization from the cell surface. Perhaps, as with AMPA subunit regulation, PICK1 brings PKC into close proximity, allowing phosphorylation of UNC5H1 followed by its dissociation from scaffold proteins. The final consequence is of course much different in the two situations. Whereas AMPA subunit internalization takes the form of long-term depression, here the loss of UNC5H1 flips the action of netrin from “negative” to “positive.” Consistent with this idea, activation of PKC caused internalization of UNC5H1 and a reduction in growth cone collapse in hippocampal neurons transfected with UNC5H1.

Behavioral/Systems/Cognitive

Breathing with the P2X3 Receptor

Pivotal Role of Nucleotide P2X3 Receptor Subunit of the ATP-Gated Ion Channel Mediating Ventilatory Responses to Hypoxia
Weifang Rong, Alexander V. Gourine, Debra A. Cockayne, Zhenghua Xiang, Anthony P. D. W. Ford, K. Michael Spyer, and Geoffrey Burnstock (see pages 11315-11321)

We monitor oxygen in our blood via highly specialized oxygen sensors called glomus cells in the carotid body. These neurosecretory cells in turn release a neurotransmitter onto afferent sensory neurons of the carotid sinus nerve. The putative transmitter in this pathway has been uncertain, because the carotid body contains several transmitter candidates. Now Rong et al. swing the spotlight on ATP. Highly specific antagonists for P2X receptors do not exist, so Rong et al. circumvented this problem by examining ventilatory responses to hypoxia in P2X2- and P2X3-deficient mice. In a ventilation chamber, hypoxia caused wild-type and P2X2−/− mice to increase their respiratory depth and frequency along with sinus nerve activity. P2X3−/− mice, however, were much less sensitive to hypoxia. Both P2X2-deficient mice had normal responses to increased carbon dioxide. The stable ATP analog αβ-metATP also induced a P2X3-containing receptor on the sensory nerve terminals.